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BIS[OXO/THIOXOTHIAZOLINYL] AROMATIC COMPOUNDS - STEREOCHEMICAL ASPECTS

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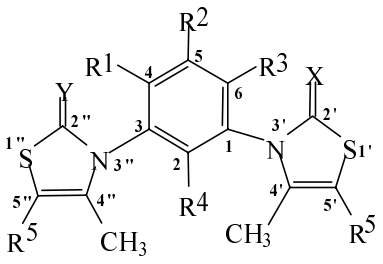
Abstract-The geometry, equilibrium compositions and barriers to rotation for the bis[oxo/thioxothiazolinyl] aromatic compounds (**1**-**4**), a series of atropisomers with two stereogenic C(aryl) – N(heterocycle) axes are reported. Comparison of the experimentally determined barriers to rotation provides information about the electronic and steric substituent contributions to the barriers, as in the series there is variation of dipoles and of substituents on the heterocyclic or the aromatic part.

The atropisomerism caused by the restricted rotation around various C-C bonds in biaryls,[1] as well as around C-N bonds in heterobiaryls and related heterocycles[2] continues to arouse interest due to their possible use as chiral ligands or auxiliaries,[3] their presence in natural compounds[4] and the possibilities they offer for evaluating steric effects.[5]

We report here the geometry, the equilibrium compositions and the barriers to rotation for the bis[oxo/thioxothiazolinyl] aromatic compounds (**1**–**4**) with the general formula **A** :



A

Compd.	X	Y	R^1	R^2	R^3	R^4	R^5
1	O	S	H	H	H	CH_3	H
2	O	O	H	H	H	CH_3	H
3	O	S	H	H	H	CH_3	CH_3
4	O	O	CH_3	CH_3	CH_3	H	H

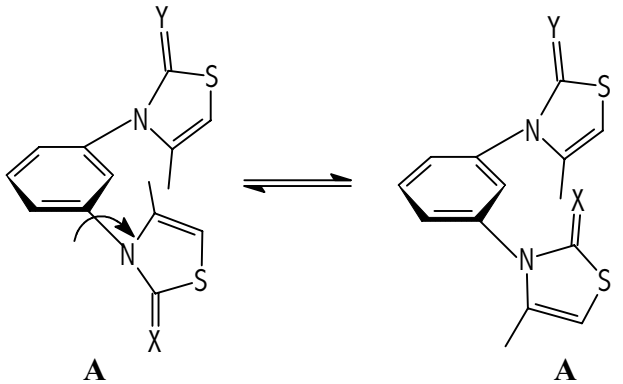
Compounds (**1**–**4**) exist as atropisomers with two C(aryl)-N(heterocycle) stereogenic axes and were

chosen from a larger series[6] in order to display : different dipoles on the heterocycles (compound (**1**) versus compound (**2**)), different substitution on the heterocyclic ring (compound (**1**) versus compound (**3**)) and different substitution on the central aromatic ring (compound (**2**) versus compound (**4**)).

Steric hindrance around the C(aryl) – N(heterocycle) bonds in compounds **A** renders the two heterocycles nonplanar with the central aromatic ring allowing two conformations:[6] *parallel* (when C=X and C=Y groups are on the same side of the central aromatic ring) and *antiparallel* (with C=X and C=Y on opposite sides of the central aromatic ring) (Scheme 1). The two conformers are diastereomers. When X = Y the *antiparallel* conformation results in a pair of enantiomers and the *parallel* conformation is a *meso* form, while when X ≠ Y each conformer results in a pair of enantiomers.

The geometry of the *parallel* conformer of **2** has been determined by X Ray analysis, the dihedral angles of the two heterocycles with the central aromatic ring being found to be 83.12° and 91.67° respectively, the deviation from the perpendicularity (from the proposed steric model for the polyarylaromatic compounds[7] both dihedral angles were expected to be 90°) being probably due to the crystal stacking.

Studies on rotational barriers as well as on atropisomer separation on microcrystalline cellulose triacetate have been reported for a series of 3-arylthiazoline-2-(thi)ones (compounds **B**, see further), representing the homologous series with a single C(aryl)-N(heterocycle) axis.[8,9] The rotational barriers, determined in diglyme by polarimetry, were of the order of 122 KJ/mole for X=O and greater than 134 KJ/mole for X=S at 360.15K. As the substitution around the chiral axes is the same for compounds **A** and compounds **B**, $\Delta G^{\neq}$ values of the same magnitude are expected for the 180° rotation of one of the two heterocycles leading to the corresponding diastereomer as shown in Scheme 1.



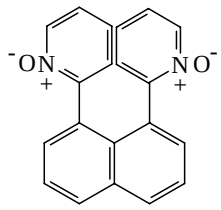
A *antiparallel* **A** *parallel*

Scheme 1

In going from the antiparallel to the parallel conformation, the probability of rotation is the same for the two heterocycles when X = Y = O (compounds (**2**) and (**4**)), while only the 'one' heterocycle (X = O) rotates in compounds (**1**) and (**3**).

Equilibrium compositions as well as barriers to rotation were experimentally determined in sealed NMR tubes in a tetrachloroethylene – deuterated chloroforme mixture (3 : 1 v/v) at 110°C, constant temperature being achieved by maintaining the tubes in boiling toluene. The tubes were retrieved at different moments, cooled at room temperature and the concentration of the two diastereomers *parallel*/*antiparallel* was obtained by integration of the corresponding ^{1}H-NMR peaks of the 4'-CH_3 groups on the heterocyclic rings. No decomposition was observed in the ^{1}H-NMR spectrum, neither in TLC (eluent $CHCl_3$: $CH_3COOC_2H_5$ 9 : 1).

The *parallel*/*antiparallel* conformational ratio could accurately be determined as for all compounds the difference $\Delta\delta_{4'\text{-}CH3} = \delta_{4'\text{-}CH3}^{antiparallel} - \delta_{4'\text{-}CH3}^{parallel} \approx 0.1$ ppm allows accurate integration (the complete assignment of ^{1}H-NMR chemical shifts was presented elsewhere[6]). The dipole values calculated with the TSAR software[10] showed a much larger value for the *parallel* conformer (7.98 D and 7.11 D for compounds (**1**) and (**2**) respectively) than for the *antiparallel* one (2.25 D and 1.61 D for compounds (**1**) and (**2**) respectively). The same situation was encountered in the case of heterocyclic atropisomers with two stereogenic axes (**5**) for which the dipole values were computed by AM1 and PM3 semiempirical methods.[11]



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In Table 1 are presented the initial composition and the equilibrium compositions of the conformer mixture, the equilibrium constant and the calculated free-energy difference ΔG° for compounds (**1**–**4**).

Table 1. Equilibrium data for compounds (**1**-**4**) (initial composition, equilibrium composition, free-energy difference ΔG°) in tetrachloroethylene – chloroform at 110°C, determined by ^{1}H-NMR

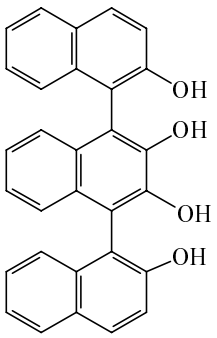
Compd	Initial composition Molar fractions x_i		Equilibrium composition Molar fractions x_e		K	$\Delta G°_{383}$
	antiparallel	*parallel*	*antiparallel*	*parallel*	x_e^{antip}/x_e^{par}	KJ/mole[a]
1	0	1	0.71	0.29	2.45	2.85
2	0	1	0.80	0.20	4.00	4.39
3	0	1	0.86	0.14	6.14	5.78
4	0.37	0.63	0.76	0.24	3.17	3.68

[a] calculated with $\Delta G° = -RT\ln K$

Experimental equilibrium compositions in Table 1 may be compared to the statistical equilibrium compositions $x_e^{stat}{}_{antiparallel} = x_e^{stat}{}_{parallel} = 0.5$, calculated using the formula :

$$x_e = \exp(-G_c/RT)/\Sigma\exp(-G_c/RT) \qquad (1)$$

which through the term G_c takes into account the conformer symmetry.[1b] Values close to the statistical compositions were found in ternaphthols (**6**) (exp. *cis* : *trans* 0.49 : 0.51).[12] In our case, there is an important difference between the experimental and the statistical values, for all compounds the equilibrium being shifted towards the *antiparallel* conformation. This situation was encountered also at the synthetic level : the synthesis of bis-thiones (in which rotation is impossible when formed), precursors of the oxygenated compounds (**1**–**4**), lead to a similar *antiparallel*/*parallel* diastereoselectivity.[6] The necessity to minimize the repulsive interaction between the two dipoles accounts for the preference for the *antiparallel* conformation.



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Comparison of experimental equilibrium compositions (Table 1) shows that a change in dipole nature (compound (**1**) versus compound (**2**)) favors less the *antiparallel* conformation than the introduction of a methyl substituent in position 5 of the heterocycle (compound (**1**) versus compound (**3**)). Introduction of methyl substituents on the central aromatic ring disfavors slightly the *antiparallel* conformation (compound (**2**) versus compound (**4**)).

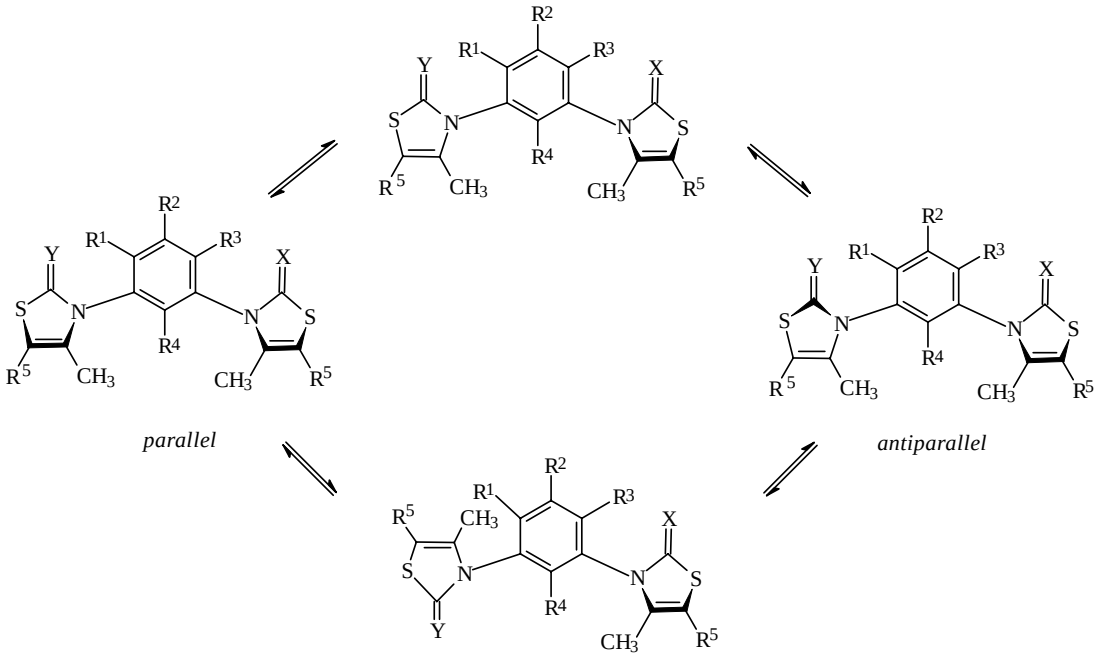
Experimental barriers to rotation $\Delta G^{\neq}$ (Table 2), were calculated from the Eyring equation,[1] the observed first order rate constant being determined from the plot of the variation of concentration over time.

Table 2. Observed reaction rates, corrected direct and reverse reaction rates and barriers to rotation for bis(oxo/thioxothiazolines) (**1**-**4**) at 110°C (solvent: tetrachloroethylene-deuterated chloroform)

Compd	k_{obs} x 10^5 s^{-1} parallel→ antiparallel	k_1^{corr} x 10^5 s^{-1} parallel→ antiparallel	k_{-1}^{corr} x 10^5 s^{-1} antiparallel→ parallel	$\Delta G^{\neq}_{corr}$ KJ/mole parallel→ antiparallel
1	6.91	2.46	1.00	125.04
2	4.02	0.81	0.20	129.03
3	13.8	5.93	0.97	122.90
4	2.41	0.46	0.14	130.67

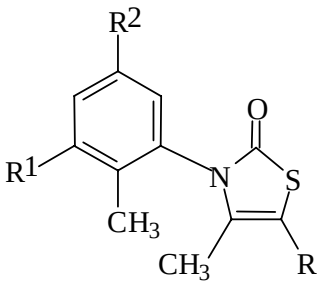
The calculated reaction rates for the direct and reverse reaction were corrected as for compounds (**2**) and (**4**) there is an equal probability of rotation of the two heterocycles and for all compounds (**1**–**4**) the *parallel* diastereomer may pass into the *antiparallel* one by two possible transition states (Scheme 2). The existence of two possible transition states has already been evidenced for the corresponding

monothiones.[9] Assuming, on steric grounds, that the two transition states are equally populated the actual rate constants will be two times lower than the observed ones for compounds (**1**) and (**3**) and four times lower for compounds (**2**) and (**4**).

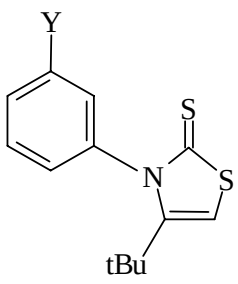


Scheme 2

Comparison of the data in Table 2 shows that introduction of a methyl group in adjacent position 5 of the heterocyclic part results in a neat decrease of the barrier to rotation (compound (**3**) versus compound (**1**)), while introduction of methyl substituents in adjacent positions on the central aromatic ring increases the barrier to rotation (compound (**4**) versus compound (**2**)). Furthermore, an important increase in the barrier to rotation is observed when replacing the "thione" heterocycle by a "one" heterocycle (compound (**2**) versus compound (**1**)). All these results may be accounted for by the electronic and steric substituent contributions to the barriers to rotation reported for the mono-[oxo/thioxothiazolinyl] aromatic compounds with general formulas **B**[8] and **C**.[9]



B



C

Enantiomerization barriers for compounds (**7a,b – 9a,b**) with general formula **B**, determined by

polarimetry in diglyme at 87°C are presented in Table 3. Data in Table 3 show that for all compounds (**7**–**9**) (with general formula **B**) the barrier to rotation is lowered by the introduction of a methyl group in position 5 of the heterocyclic part (compounds **b** versus compounds **a**), fact which is due mainly to the electronic contribution, the buttressing effect being less important in the case of five-membered rings. The same situation is illustrated by compounds (**3**) and (**1**) in Table 2, the difference being more important.

Table 3. Enantiomerization barriers for compounds (**7a,b**–**9a,b**) (general formula **B**; **a** R = H, **b** R = CH_3) at 87°C determined by polarimetry (solvent: diglyme)

Compd	R^1	R^2	$\Delta G^{\neq}$ kJ/mole
7a	H	H	122.0
7b			121.7
8a	CH_3	H	130.9
8b			129.9
9a	H	CH_3	123.3
9b			122.6

Introduction of a methyl group in buttressing position on the central aromatic ring increased dramatically the barrier to rotation (compound (**8**) versus compound (**7**)), while introduction of the methyl in non-buttressing position (compound (**9**) versus compound (**7**)) increased the barrier to rotation only slightly. The introduction of two additional methyl groups on the central aromatic ring (compound (**4**) versus compound (**2**)) had not such a dramatic effect on the barrier to rotation due to the levelling of the buttressing effect.

The barriers to rotation (determined by polarimetry in ethanol) for compounds with general formula **C** (for Y = Cl, $\Delta G^{\neq}_{339.4}$ = 104.19 kJ/mole; for Y = $N(CH_3)_2$ $\Delta G^{\neq}_{339.4}$ = 107.75 kJ/mole) showed[9] that electron accepting substituents Y at the meta position significantly decrease the barrier to rotation. This remark accounts for the lower barrier to rotation in **1** versus **2**, considering the second heterocycle as being the substituent Y. The accepting ability is larger in the thioamide-like than in the amide-like framework due to the larger positive character of the nitrogen in the former structure.[13]

REFERENCES

1. a) M. Oki in “Topics in Stereochemistry”, Vol. 14, ed. by N. L. Allinger, E. L. Eliel, and S. H. Wilen, Wiley, New York, 1983, p. 1.

b) “Stereochemistry of Organic Compounds”, ed. by E. L. Eliel and S. H. Wilen, Wiley, New York, 1994.

2. Z. Aksaç, E. Pinar, and S. Içli, *Org. Magn. Reson*., 1983, **21**, 548; A. Mannschreck, H. Koller, G. Stuhler, M. A. Davies, and J. Traber, *Eur. J. Med. Chem. Chim. Ther.*, 1984, **19**, 381; C. Roussel, M. Adjimi, A. Chemlal, and A. Djafri, *J. Org. Chem*., 1988, **53**, 5076; M. Mintas, V. Mihaljevic, H. Koller, D. Schuster, and A. Mannschreck, *J. Chem. Soc., Perkin Trans. 2*, 1990, 619; I. Dogan, N. Pustet, and A. Mannschreck, *J. Chem. Soc., Perkin Trans. 2*, 1993, 1557; K. Saito, M. Yamamoto, and K. Yamada, *Tetrahedron*, 1993, **49**, 4549; D.P. Curran, H. Qi, S. J. Geib, and N. C. De Mello, *J. Am. Chem. Soc*., 1994, **116**, 3131.
3. H. Brunner, G. Olschewski, and B. Nuber, *Synthesis*, 1999, **3**, 429; X. Dai, A. Wong, and S. C. Virgil, *J. Org. Chem*., 1998, **63**, 2597; O. Kitagawa, H. Izawa, K. Sato, A. Dobashi, T. Taguchi, and M. Shiro, *J. Org. Chem*., 1998, **63**, 2634.
4. A. Ino, and A. Murabayashi, *Tetrahedron*, 1999, **55**, 10271.
5. R. Gallo, C. Roussel, and U. Berg, *Adv. Heterocycl. Chem*., 1988, **43**, 238.
6. A. Hîrtopeanu, C. Suteu, C. Uncuta, G. Mihai, and C. Roussel, *Eur. J. Org. Chem*., 2000, 1081.
7. R. Willem, M. Gielen, C. Hoogzand, and H. Pepermans in “Advances in Dynamic Stereochemistry”, Vol. 1, ed. by M. Gielen, Freund Publishing House Ltd., London, 1985, p. 207.
8. C. Roussel, J. L. Stein, and F. Beauvais, *New J. Chem*., 1990, **14**, 169.
9. C. Roussel, and A. Djafri, *New J. Chem*., 1986, **10**, 399.
10. TSAR 3.0 software from Oxford Molecular Group (Silicon Graphics station 02R10000)
11. J. A. Zoltewicz, N. M. Maier, and W. M. F. Fabian, *J. Org. Chem*., 1997, **62**, 2763.
12. M. Belohradsky, M. Budesinsky, J. Gunterova, J. Hodacova, P. Holy, J. Zavada, I. Cisarova, and J. Podlaha, *J. Org. Chem*., 1996, **61**, 1205.
13. J. Sandström, “Dynamic NMR Spectroscopy”, Academic Press, London, 1982.